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| EXAMINER | |
|---|---|
| DAVIS, MINH TAM B | |

| ART UNIT | PAPER NUMBER |
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| 1642 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

| Advisory Action Before the Filing of an Appeal Brief | Application No. 10/650,608 | Applicant(s) CASSART ET AL. | |
|---|---|---|---|
| | Examiner MINH-TAM DAVIS | Art Unit 1642 | |

*--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

THE REPLY FILED 18 July 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *18 July 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: *none*.
   Claim(s) rejected: *7-9*.
   Claim(s) withdrawn from consideration: *none*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 5. Applicant's reply has overcome the following rejection(s): The entire 112, first paragraph, written description, and part of 112, first paragraph, enablement concerning the ASCL2 variants.

## *DETAILED ACTION*

Applicant cancels claim 6.

**Accordingly, claims 7-9, SEQ ID NO: 25, are being examined.** The embodiment of claims 7-9, as drawn to a method for inducing an immunoresponse, using SEQ ID NO: 16-24, 26-33 have been withdrawn from consideration, as being drawn to non-elected invention.

### *Rejection Withdrawn*

The entire 112, first paragraph, Written Description rejection, and a section of 112, first paragraph, Enablement rejection, concerning the issue of ASCL2 variants, have been withdrawn, in view of the amendment.

### *Claim Rejections - 35 USC § 112, First Paragraph, Enablement*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9 remain rejected under 35 U.S.C. 112, first paragraph, because the specification and the claims lack enablement for a method for inducing an immune response to SEQ ID NO:2 in a human, or non-human animal, using a peptide fragment of SEQ ID NO:2, i.e. SEQ ID NO:25, for reasons already of record in paper of 04/18/07.

The response asserts that the claim interpretation as encompassing a method for treating cancer is legally incorrect, reading into a claim unclaimed results, because the claims do not recite a step of successfully treating cancer, nor an endpoint of tumor reduction.

The response has been considered but is not found to be persuasive for the following reasons:

The claims are **reasonably interpreted** as a method for **treating cancer**, as contemplated in the specification, via inducing an immune response. Such interpretation does not require rigorous standards of clinical trials. For example, the encompassed method is also for an animal model having cancer, and the results do not necessarily require tumor regression, but only inhibition of cancer cell growth in vivo in a cancer patient. The encompassed method for treating cancer is not enabled, because of the unpredictability of cancer treatment, including cancer treatment using a CTL epitope, in view of the teaching of Kirkin et al, Boon, Gaiger et al, Ezzell et al, and Spitler et al, all of record.

Further, the issue that one cannot predict whether the claimed peptide SEQ ID NO:25 could even induce a **sufficient immune response *per se*** in **a cancer patient** for any practical use as contemplated in the specification, has been also addressed. That is, one cannot predict that the claimed method would induce sufficient CTL response or production of an antibody to SEQ ID NO:2 in a cancer patient, using the peptide SEQ ID NO:25, for any practical use, in view of the teaching of :

1) Smith et al, of record, that tumor antigen overload blocks specifically either cytotoxic or proliferative responses of tumor specific T cells, and that loss of MHC representation at the surface of the cancer cell severely limits the possibilities for cytotoxic T cells to find said tumor specific antigen in the necessary MHC context, and

2) White et al, of record, that antigen internalization or downregulation in cancer cells cause the disappearance of the antibody target.

Concerning the argument that SEQ ID NO:25 could be used as an adjuvant, or in adoptive immunity, the specification does not contemplate such use, nor such limitation is recited in the claimed method. Therefore, the argument is moot.

The following is the detailed discussion of the cited references.

Rosenberg et al recited by the response.

Concerning the teaching of Rosenberg et al that the scarcity of the clinical response of patients to peptide vaccination makes it difficult to validate the usefulness of sensitive in vitro technique to detect the **in vivo generation of anti-tumor T cells** (p.909, last paragraph, last four lines, and abstract), the response asserts that the claims are only limited to inducing an immune response, there is no required clinical end point. The response asserts that the data in Rosenberg et al showing only a few peptides produce an effective clinical response in patients is not germane, because the claims are only limited to inducing an immune response.

The response has been considered but is not found to be persuasive for the following reasons:

The claims are **reasonably interpreted** as a method for **treating cancer**, as contemplated in the specification, via inducing an immune response, supra.

Further, Rosenberg et al discuss difficulty to extrapolate from in vitro data to detection of the **in vivo generation of anti-tumor T cells,** which clearly is an immune response, and is necessary for inhibiting cancer cell growth or tumor regression. In addition, the teaching of Rosenberg et al confirms the teaching of Kirkin et al that only a few peptides actually could induce response to the antigen in vivo, resulting in tumor regression (Kirkin et al , abstract).

Since only a few peptides actually could induce response to the antigen in vivo, one cannot predict which other peptides, including the claimed SEQ ID NO:25 could induce a response to the antigen in vivo in cancer patient, resulting in inhibiting cancer cell growth.

The response further asserts that Rosenberg et al also teach the use of adjuvants to increase the numbers of T cells with high avidity, which therefore, is also in agreement with the disclosure in the specification.

The response has been considered but is not found to be persuasive for the following reasons:

The claims do not recite the use of adjuvants with SEQ ID NO:25, therefore, Applicant argues limitation not in the claims.

Tsuruma cited by the response

The response asserts that Tsuruma et al teach that vaccination of a peptide together with an adjuvant, right after surgery, induces a prolonged relapse free interval in melanoma patients.

The response has been considered but is not found to be persuasive for the following reasons:

The claimed are not drawn to a method for inducing an immune response, using SEQ ID NO:25 and an adjuvant. Thus, the response argues limitation not in the claims.

Further, although an adjuvant has been shown to enhance the immune response of a peptide, however, since not any peptide are rendered effective in treating cancer by the presence of an adjuvant, as evidenced by the fact that thus far only a few CTL peptides are successful in

cancer treatment, as taught by Kirkin et al, and Rosenberg et al, one cannot predict which CTL peptides, including the claimed SEQ ID NO:25, would be effective in treating cancer.

Moreover, Tsuruma confirms the problems with immunotherapy taught by Smith et al, i.e. escape of cancer cells from the host immune system, such as downregulation of the expression of tumor antigens, or MHC molecules, loss of the ability to present the antigen to T cells, or production of suppressive cytokines (p.805, first column, last paragraph). Such problems would not predictably be overcome by adding an adjuvant. For example, adding an adjuvant would not predictably solve the problem of lack of target cancer cells for T cells to bind to and produce an immune response, due to downregulation of the expression of tumor antigens, or MHC molecules.

Hoos et al cited by the response

The response asserts that Hoos et el. stands for the principle that tumor regression is an inappropriately restrictive endpoint by which to assess an immunotherapeutic, The response asserts that thus, Hoos et el. is highly relevant evidence that shows that the endpoint selected by the Office Action is not appropriate for judging the enablement of Applicants claimed methods for inducing an immune response.

The response has been considered but is not found to be persuasive for the following reasons:

The claims are **reasonably interpreted** as a method for **treating cancer**, as contemplated in the specification, via inducing an immune response, supra.

Further, since treating cancer only requires inhibition cancer cell growth in a cancer patient, and not necessary skrinkage of tumor or slowing the rate of tumor regression, Hoos et al teaching is not applicable here.

The response requests clarification of the following statement in the previous Office action: "Concerning the response's comment that methods involving immunogenic fragments of polypeptides are useful as an adjuvant to other therapeutic modalities, and that immunogenic fragments are useful in non-vaccine settings, such as adoptive immunity, the response argues limitation not the claims".( See page 5 of the present Office Action).

That statement means that "since the claims do not recite that the claimed method induces an adjuvant effects for other therapeutic modality, such as chemotherapy, the argument that the claimed peptide SEQ ID NO:25 is useful as an adjuvant for other therapeutic modalities only addresses a limitation not in the claims, and thus the argument is moot".

In response to the issue that there is no indication that the claimed peptides actually have any adjuvant effects, enhancing the effectiveness of other therapeutic modalities, such as conventional chemotherapy, the response asserts that essentially, the Office Action is requiring that Applicants demonstrate efficacious cancer treatment, which goes far beyond the legally supportable standard for enablement of a method for inducing an immunoresponse.

The response has been considered but is not found to be persuasive for the following reasons:

An adjuvant effect needs only enhancing the effect of other therapy, such as chemotherapy. Thus, the issue of whether the claimed peptide could enhance the effect of other therapy is not beyond the legally supportable standard for enablement.

White et al

The response asserts that the Office statement that "...due to internalization or down-regulation of the antigen or the MHC molecules, the antibodies or the T cells would not be able to recognize the target cancer cells, and thus would not be effective or useful for therapeutic application, is speculative and under the Rules cannot be relied upon to support the rejection without an affidavit. The response asserts that moreover, it is still irrelevant to Applicants' claimed method, which includes neither a clinical efficacy endpoint nor a repeat dosing step.

The response has been considered but is not found to be persuasive for the following reasons:

It is well known in the art that an antibody or a T cell functions via binding to the target antigen present on the target cell, in conjunction with the MHC molecule (Roitt et al, of record). Thus, one would reasonably expect that with internalization or down-regulation of the antigen or the MHC molecules, the antibodies or the T cells would not be able to recognize the target cancer cells, and thus would not be effective or useful for treating cancer. Therefore, an affidavit is not necessary.

Gaiger et al and Oka et al

The response assert that the Office now replies that Oka et al is not germane. The response asserts that both Gaiger et al and Oka et al show that the peptides of WT-1 are immunogenic. The response asserts that the instant claims do not recite tumor regression end point, but only inducing an immune response, which is all that must established.

The response has been considered but is not found to be persuasive for the following reasons:

The response misinterprets the Office action. The Office action did not state that Oka et al is not germane. The Office action states that the WT-1 peptide taught by Gaiger et al is different from that taught the teaching of Oka (previous Office action, p.7, third paragraph). In other words, the teaching of Oka et al does not contradict the teaching of Gaiger et al, because although the WT-1 peptide taught by Oka et al is effective in inducing cancer regression, the WT-1 peptide taught by Geiger et al, which although show in vivo CTL response, but is not effective in treating cancer, is different from that taught the teaching of Oka (previous Office action, p.7, third paragraph).

Further, although inducing CTL response in vivo, the WT-1 peptide taught by Gaiger et al does not have any effect on cancer growth in vivo, thus demonstrating that even the ability to inducing a CTL response in vivo does not necessarily lead to any result of any practical use.

Finally, concerning the issue that one could not predict that SEQ ID NO:25 would be recognized by CD4+T cells because SEQ ID NO:25 is only 9 amino acids and CD4+T cells typically bind longer peptides, the response asserts that the claim language "comprising"

modifies the term "an epitope of SEQ ID NO:2.", and thus, the claim does not exclude fragments or peptides longer than the epitopes of SEQ ID NO: 25.

The response has been considered but is not found to be persuasive for the following reasons:

The claimed method encompasses a method for inducing immunoresponse, using a genus of peptide fragments of any size, provided they comprise the 9 amino acid peptide SEQ ID NO:25. It is noted that the CD4+ T cell epitope is more than 12 amino acids as taught by Roitt et al, of record. However, there is no indication that SEQ ID NO:25 is the core sequence of the CD4+ T cell epitope, which core sequence by itself is sufficient and confers the recognition by CD4+ T cells. Further, there is no indication that amino acid sequences comprising SEQ ID NO:25 and are longer than 12 amino acids would induce CTL response, in view that native amino acids flanking a CTL epitope could have unpredictable effect on the function of the core CTL epitope. Thus, although amino acids 97-111, and 93-107 of SEQ ID NO:2 in Example 10, which encompass amino acids 90-98 of SEQ ID NO:2 (i.e. SEQ ID NO:25) (see information on pages 6, 10-11 of the communication of 09/26/06), induce CD4+ T cell response, one cannot predict that the claimed numerous peptides comprising SEQ ID NO:25 would induce CD4+ T cell response.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 29, 2007

/Larry R. Helms/
Supervisory Patent Examiner